DECLARATION 1

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

This Declaration is being made in order to distinguish the claimed invention from the teachings of the references Hollingsbee et al. (WO 97/02845) and Tsubouchi et al. (US 6,175,053) cited in the claim rejections according to § 103.

1. The subject-matter of the objected patent Tsubouchi is a wound dressing that is based on a protein material (fibroin and sericitin) that is fully biocompatible and has a very good water absorption properties which results in the material not adhering to the wound. Various additives (disinfectants and others) are added to this basic material. The examples of disinfectants include, among others, iodine, potassium iodide, hydrogen peroxide and povidon iodine. However, it is to be noted that it is not clearly described what exactly was used as a disinfectant in case of a film. Iodine and potassium iodide are presented separately, separated by a comma. The agent that may be used as a disinfectant is actually a solution of iodine in potassium iodide (not iodine or potassium iodide separately). The mixture of iodine and potassium iodide in a solution gives rise to potassium triiodide which releases elementary iodine that is the very disinfectant. If iodine and potassium iodide were used separately then potassium iodide has no disinfecting effects, and iodine does not dissolve in the concentration that the presence of a disinfectant is presented (e.g. column 3, lines 9-12); the claims do not mention the amount of disinfectants at all. It is most likely that the author of the patent included the above mentioned disinfectants without even trying whether it is possible to prepare such a film.

   Even if we admitted that the author of the patent did mean the solution of iodine in potassium iodide, the truth is that it is impossible to prepare a film containing iodine, resp. iodine with potassium iodide as a disinfectant in an equilibrum by means of the processes described in the patent. The substance of the problem lies in that the preparation of the film requires its drying. The description discloses (e.g. column 7, lines 60 – 67; column 9, line 46 – column 10, line 3) that the solution of proteins the film was being prepared of was, together with the disinfectant, cast on a horizontal acrylic resin plate and dried at room temperature. If said solution contained the solution of iodine in potassium iodine, then one must realize that the triiodide does not exist in the solid state, it decomposes to iodine and potassium iodide while iodine gradually evaporates at the film drying conditions and thus moves the equilibrum that exists in the solution between iodine, iodide and triiodide (iodine + iodide → triiodide) towards the triiodide decomposition. This leads to an effect where there is no iodine in the film within a certain time, resp. if iodine is present then just in a trace amount that is not able to exhibit disinfecting properties. Regarding the fact that we have examined the question of stability of iodine in a potassium iodide solution very thoroughly, we have the information on the rate of iodine volatilization – please see graph 1 (Enclosure I) showing the volatilization

of iodine from the solution of iodine in potassium iodide which is enclosed; it can be clearly seen therefrom that in 24 hours there is only 20 % of the initial amount of iodine in the solution. That means that iodine could not be present as a disinfectant in the film. In such a case a question arises as to whether a patent disclosing something unable to be prepared and even contradicting the physical laws may be objected as a state of the art. Moreover, please note the paragraph [0026], of US 2005/0181025 A1, with an explanation of why iodine alone cannot be used in a solution.

The same applies to hydrogen peroxide that is stated as a disinfectant in a dry film as well. According to our opinion, hydrogen peroxide does not exist in a dry film and if there were some traces thereof, it would be improper to call it a disinfectant. We believe that the author of the patent had neither examined said substances as disinfectants nor proved that the film containing them really had disinfecting effects, actually we suppose he just simply included them into the description.

Example 4 of Tsubouchi (US 6,175,053, column 13) describes a preparation of a film containing povidon iodine. Povidon iodine is an organic compound which is totally different from an inorganic complex potassium triiodide, and the fact that both contain iodine atoms does not imply that they might be classified as similar compounds. Povidon iodine has different biological effects in the mixture with hyaluronate and thus, cannot be freely interchanged with other iodine compounds.

Now, as far as the difference between the Tsubouchi document and our invention is concerned, it lies in that Tsubouchi discloses the use of a wound dressing material containing fibroin and sericitin – there is no mention of hyaluronic acid. In our case, while examining the interaction of iodine and potassium triiodide with various polysaccharides, we found out that the hyaluronate solution is partly stabilized by iodine in the solution and forms mixtures therewith that have a totally unexpected favorable effect on wound healing. It showed up that the other polysaccharides tested (6 in total), not even oxycellulose the structure of which is similar to the one of hyaluronate, do not have similar properties to those of hyaluronate in the mixture with iodine complex. The disinfecting properties of iodine complex were just advantageously used in the hyaluronate stabilization. The hyaluronate stabilization lies in its ability to inhibit bacteria that decompose the hyaluronate very fast. Iodine and potassium iodide form potassium triiodide in a solution which is unstable as well due to the volatility of iodine but when using a diluted solution of iodine and potassium iodide, the equilibrum is moved towards the free iodine. Therefore, the diluted potassium triiodide makes the hyaluronate stable and thus the wound healing properties thereof may be exerted. Moreover, a synergistic effect of this mixture was proved: a mixture of hyaluronate with potassium triiodide healed the wound much faster than the hyaluronate without potassium triiodide (see graph 2 – Enclosure II, and fig. 1 – Enclosure III). Potassium triiodide itself, without hyaluronate, showed a tendency to act in a rather inhibitory manner, it did not positively influence the wound healing at all. Moreover, our studies showed that the use of hyaluronate with potassium triiodide enhances the growth of granulation tissue forming in the wound and results in an increase of glycosaminoglycanes amount in this granulation tissue (see [0025] and [0026] of US 2005/0181025 A1). It is to be noted that the granulation tissue formation is the second, very important step in the wound healing. Therefore, the acceleration of the granulation tissue formation leads to an acceleration of the wound healing. Neither the hyaluronate alone, nor the potassium triiodide complex alone are able to produce an increased amount of the granulation tissue (see graphs 2a-b, Enclosure IV).

2. Hollingsbee et al. teach compositions of hyaluronic acid having molecular weights between 50,000 to 2,000,000 and they teach that the hyaluronic acid can be in a salt form, specifically sodium salt, and that antimicrobial agents may be added to hyaluronic acid, such as polyvinylpyrrolidone iodine. The iodine – potassium iodide complex is not mentioned at all because iodine would volatilize from the film (see the explanation above and [0026] of US 2005/0181025 A1). The Hollingsbee's mixture of hyaluronate with povidon-iodine does not exhibit any positive effects on wound healing that could be comparable to the effects of the mixture of hyaluronate with iodine + potassium iodide complex. In Hollingsbee, there is no mention of any positive effect of the mixture of hyaluronate with povidon-iodine on the rate of wound healing, on the granulation tissue formation and the like. Neither does the technical literature mention any effects of the mixture of hyaluronate with povidon-iodine similar to those of a combination of hyaluronate with iodine + potassium iodide complex. Moreover, according to the results of the tests that we performed in developing a new wound-healing preparative, povidon-iodine in the mixture with hyaluronate showed no exceptional effect on wound healing such as the solution of iodine in iodide did. Povidon-iodine is considered to be a disinfectant only which is not the case of the solution of iodine in potassium iodide the main function of which is hyaluronate stabilization (see the explanation above). Povidon iodine is a totally different compound, has different biological effects in the mixture with hyaluronate and thus, cannot be freely interchanged with iodine compounds.

   Further, we would like to point out that the patent document WO 97/02845 of Hollingsbee was objected in the international search report and was classified as an "A" document, i.e. a document defining the general state of the art which is not considered to be of particular relevance (see Enclosure V).

3. In the Office Action, p. 5-6, it is objected that since potassium (or sodium) iodide and iodine are both extremely well known in the art for their disinfecting ability, it would have been obvious to one of ordinary skill in the art at the time of the invention to use said solution as a disinfectant for treating wounds. A real person skilled in the art of wound healing knows that the solution of iodine in potassium (or sodium) iodide had been used for wound disinfection in the 19th century and in the beginning of the 20th century, i.e. in a time when no other disinfecting preparative having the same or similar efficiency had been known. Early after its introduction to use it showed up that such a solution is very unstable, exhibits very irritable properties to the wound, its application causes pain to the patients, it doesn't support the wound healing and, moreover, it colors the surrounding skin and textile that it comes into contact with very strongly [see Enclosure VI: R.A.Cooper: Iodine revisited, Int Wound J 4, 124-137 (2007)]. Efforts to substitute the solution of iodine in potassium iodide by another disinfectant that would be more suitable for wound healing had been made a hundred years ago[see Enclosure VII: H.D.Dakin: On the use of certain antiseptic substances in the treatment of infected wounds, Brit J Med 318-320 (1915)]. The attempts to replace the solution of iodine in iodide by another agent had continued until 1949 when the first practically utilizable iodoform on the basis of polyvinylpyrrolidone which has been used since then was discovered. The doctors' opinion of the solution of iodine in iodide is clearly expressed in the article by F.C. Kelly in which he says: "END OF AN ERA. Last and perhaps greatest protagonist of direct energetic iodine disinfection of wounds was Sir LEONARD ERSKINE HILL, F.R.S. (1866-1952) director of research, St. John Clinic and Institute of Physical Medicine, London. Convinced iodine veteran of World War I, he returned to its defence on outbreak of World War II, extolling virtues of intensive iodine disinfection of wounds 'in all their depths and ramifications'. Views not accepted by the moderns. With

him died finally the 1914-1918 war faith in the iodine 'first field dressing'." [see Enclosure VIII: F.C.Kelly: Iodine in medicine and pharmacy. Since its discovery – 1811 – 1961, Proc Royal Soc Med, 54, 831-836 (1961)]. After the discovery of the complex of polyvinylpyrrolidone with iodine (povidon iodine, PVP-iodine) the use of the solution of iodine in iodide ceased because it was replaced by a much better preparative that eliminated all of the above mentioned negative features of the solution of iodine in iodide and, moreover, it proved itself 3x safer than the solution of iodine in iodide [see Enclosure IX: H.A. Shelanski, M.V. Shelanski: PVP-iodine: history, toxicity and therapeutic uses, J Internat Coll Surgeons, 25, 727-734 (1956)]. Therefore, in view of all of the above mentioned facts, the solution of iodine in iodide had to be used as a disinfectant to wounds in spite of its adverse effects only until a substitute for this solution was found which had no adverse effects and, moreover, was less toxic and thus safer. We are convinced that nowadays, when a broad spectrum of antibiotics, cationic antimicrobial agents, antimicrobial peptides and many other newer, safer and more effective disinfectants are available, a real expert in this subject field would hardly revert to the solution of iodine in iodide as a disinfectant. Firstly, he would have to face the problems of negative organism reactions to the preparative, secondly, he would have to deal with the higher toxicity and further, he would have to eliminate the lack of stability of the solution. If someone reverts to the solution of iodine in iodide, it is for other reasons than its disinfecting ability, such as we did it.

Moreover, the fact that no patent application (except of ours) claiming a use of a mixture of hyaluronate with a solution of iodine in iodide has been filed up till now clearly shows that a mixture of hyaluronate with a solution of iodine in iodide is not something that would occur to a person skilled in the art and that simple mixing of said substances would suffice.

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DECLARATION 2

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

This Declaration is being made in order to overcome the claim rejection according to 35 USC § 112.

The Examiner objects that the Applicant "has not shown any ability of the composition to lessen, much less prevent adhesion of the wound covering to the wound" and "has most definitely not shown how one of skill in the art would use this invention to prevent wound adhesion".
On the basis of our experimental results we have found out that the wound treated by the mixture of hyaluronate with potassium triiodide maintains a significantly greater amount of hyaluronate and said hyaluronate has a higher molecular weight compared to the hyaluronate present in the wound treated by hyaluronate alone. The experiment conditions were as follows: A shaved space on the back side of rats was cleaned by the distilled water and by the disinfectant AHD 2000. An excisional square wound was made by a scalpel and scissors. One of the following: a physiological solution, a solution of iodine complex (the same final concentration as in our preparation Hyiodine, containing hyaluronic acid with potassium triiodide), sodium hyaluronate (the same final concentration as in our preparation Hyiodine) and the mixture of hyaluronate with iodine complex (Hyiodine) was applied in 1 ml dose. In case of a round wound, a ring having the diameter of 2 cm was quilted in the round wound. All wounds were covered by a sterile gauze and the square ones were covered by elastic bandages in addition. The process of wound preparation is documented on figs. 2 a-d (Enclosure X). The surface of the wound was evaluated in selected time intervals. The quantification of the hyaluronate that remained within the wound was very difficult as the hyaluronate layer had to be scraped off without taking the granulation tissue which is extremely soft along. The results thus obtained were quite dispersed. However, visually it was clear that the wound that was treated by the mixture of hyaluronate with potassium triiodide contained more hyaluronate than the wound that was treated by hyaluronate alone. In a clinical investigation we have found out that the bandage that was applied together with the mixture of hyaluronate with potassium triiodide could be kept on the wound for 60 hours without adhering to the wound. In case of the application of hyaluronate alone (without potassium triiodide) some of the bandages started to adhere after 24 hours already and practically all of them were stuck to the wound within 48 hours. Moreover, we have measured the molecular weight of the hyaluronate in the wound. It is known that hyaluronate having a higher molecular weight has a greater ability to retain water and thus prevent the adhesion. It was proved that after the application of the mixture of hyaluronate with potassium triiodide, the molecular weight of hyaluronate decreased significantly more slowly than in case of the application of the hyaluronate only. The graph 3 (Enclosure XI) shows that the hyaluronate that was not applied in the mixture with potassium triiodide almost disappeared from the wound within 30 hours (its molecular weight was very strongly reduced). Therefore, the conclusion is that the hyaluronate in a combination with potassium triiodide according to the invention persists on the wound surface much longer than the hyaluronate alone (the hyaluronate molecular weight when in combination with potassium triiodide decreases much

more slowly than the one of the hyaluronate alone) and that is why the wound surface is moist for a longer time. This provides for a suitable environment for moist healing, prevents the sticking of the bandage to the wound and also the hyaluronate persisting on the wound surface increases the concentration of some healing factors within the wound. The main subject-matter of the invention lies in a preparation which provides for an ideal environment needed for the formation of the granulation tissue and other regeneration processes in the wound and prevents the adhesion of the bandage to the wound.

Regarding the objection that the Applicant has not shown how one of skill in the art would use this invention to prevent wound adhesion, please note [0013] and [0014] of US 2005/0181025 A1 which explicitly state the method of applying the composition. The paragraph [0013] mentions a direct or indirect application of the composition, while the indirect application is explained as an application "on a wound-contacting portion of a bandage". The paragraph [0014] further discloses that "A hyaluronic acid, iodine and potassium iodine composition is provided to a wound and covered, or the composition is applied to the wound covering, which is then applied to the wound". The results of the tests performed in order to examine the adhesion of the bandage to the wound were already mentioned above.

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